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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

| EXAMINER | |
|---|---|
| SPECTOR, LORRAINE | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/731,595 | KOREN ET AL. | |
| | Examiner | Art Unit | |
| | Lorraine Spector, Ph.D. | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23,25-27,29,30,32-35,37-40 and 42-50* is/are pending in the application.

4a) Of the above claim(s) *26,27,29,32,34,36,37,40-42 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25,30,33,35,38,39,43,45-48 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *23,25-27,29,30,32-35,37-40 and 42-50* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/2008*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

## DETAILED ACTION

Claims 23, 25, 30, 33, 35, 38-39, 43 and 45-48 and 51 are under consideration.

Newly submitted claim 49 is withdrawn from consideration as being drawn to a non-elected species, there being no allowable generic claim.

The rejection of claims 23, 33, 35, 38, and 43-48 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5641655 (Foster et al.) is withdrawn in view of applicants amendments.

### *Claim Objections*

Claim 44 is improperly dependent as a nucleic acid does not further limit the protein it encodes. Applicants amendment to the claim has not addressed this objection.

Applicants are reminded that the elected species is a deletion of residues 339-353 of human TPO. Claims 32, 35, 43 and 45-48 (by dependency) as amended are objected to for encompassing non-elected species, there being no allowable generic claim.

Claim 39 as amended is objected to for reciting "deletion of amino acid sequence of SEQ ID NO: 1". The word "the" should be inserted between "of" and "amino" to be remedial.

Appropriate correction is required.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 30 remains rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11, 12, 25 and 26 of U.S. Patent No. 6,673,580. Although the conflicting claims are not identical, they are not patentably distinct from each other because although there are minor differences in the wording of the claims (in fact rendering the instant claims indefinite), the claims are clearly substantially overlapping, and the instant claims fall within the scope of the patented claims.

It is noted that in the response filed 5/16/2008 that applicants have requested that this rejection be held in abeyance until notice of allowable subject matter. The Examiner notes that claim 33 cannot be indicated as allowable until this matter is resolved. Further, should applicants intend to traverse this rejection on its merits, it must be done in the next response. Any further delay in traversal will not be considered timely.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 30, 33, 35, 38, 39 and 43-44 and 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 30, and 51 are indefinite because they claim a therapeutic polypeptide with reduced immunologic activity without specification of the peptide in question, or specifically where it is modified. The claims are drawn to a concept, rather than to a particular polypeptide or set of polypeptides. As such, the metes and bounds of the claims cannot be determined, and no meaningful search of the prior art can be performed. For the purpose of compact prosecution,

the claims will be interpreted as reading upon the elected species in applying the prior art. See also the rejection of the same claim under 35 U.S.C. §112, first paragraph for lack of adequate written description, below. Applicants argue that there is sufficient written description of this claim, and therefore that the claim is not indefinite, and that breadth does not, in and of itself constitute indefiniteness. This argument has been fully considered but is not deemed persuasive because it remains that a person of ordinary skill in the art reading the claim cannot envision what specific molecules are or are not within the metes and bounds of the claim. The claim is a a single means claim, wherein there is description only of TPO in the specification, whereas applicants seek coverage of all possible modified therapeutic polypeptides that have a modification in an immunodominant epitope causing a reduced immune response while maintaining therapeutic value. Such are not described, and the claim is indefinite because the metes and bounds cannot be determined, nor can a meaningful search of the prior art be performed.

The recitation of the claims of the term "modified" is taken to be a product by process limitation, indicating that there was a 'starting' polypeptide that has been altered to conform with the claimed limitations. As such, the limitation is only given weight to the extent that it dictates the structure of the claimed polypeptide. In those claims where no specific 'starting' polypeptide is designated, the limitation can be given no weight, and the claims are indefinite. For example, see claims 23, 25, 33, and 51, for example. Applicants argue that the amendment of the claims to state that they "now refer to modification of an unmodified therapeutic polypeptide". This argument has been fully considered but is not deemed persuasive because it remains that without knowing what the "unmodified" peptide was, one could not determine whether it had been modified or not. For example, it is well known in the art that there exist many forms of particular proteins, due to genetic variation in populations. Therefore, there may be naturally occurring "modifications"; one cannot tell, being given only the protein in a tube, whether it has been modified or not, without knowing what the starting material was. Further in applicants traversal, applicants refer to amendments of non-elected species, the claims having been withdrawn from prosecution. Such arguments are moot at this time.

Further, the recitation "modification only in an immunodominant epitope" is indefinite, as it is not clear whether, if the modification is a deletion, that deletion may delete additional

sequence, or is limited to the immunodominant epitope. With respect to the recitation that the modification is *only* in an immunodominant epitope it is noted that the specification breathes no life and meaning into this term. While terms are, in the absence of further definition to be given their ordinary meaning, it appears that applicants intend more than "within", as the claims also allow deletion of the entire epitope. Also, as it is well known in the art that epitopes may be discontinuous, the meaning of "within" an epitope is further indefinite as it is not clear whether the alteration is restricted only to those amino acids that comprise the epitope, or could involve intervening amino acids. Further, if, for example, residues 339-353 *are* an immunodominant epitope, it is not clear how deletion of that entire sequence could be construed as a modification *in* that immunodominant epitope. Applicants traversal does not address this point. Applicants allege that "within" should be given its plain and ordinary meaning. However, as set forth in the previous Office Action and in this paragraph, deletion of an entire epitope cannot be construed to be a deletion "within" that epitope, though such is clearly envisioned in the specification.

Claim 30 is an incomplete method claim. The identification of the immunodominant epitope is essential to the invention. The claim has been amended to recite that the identification is done by "contacting" the polypepide or fragments thereof with an antibody or population thereof from a naive human or animal or population thereof. Applicants point to the paragraph bridging pages 13-14 of the specification for basis for such. However, it remains that such description does not recite sufficient method steps. Merely "contacting" will not detect immunodominant epitopes. Antibodies from a naïve population might or might not react with immunodominant epitopes, they might react with non-immunodominant epitopes. In fact, the specification at page 18 lines 5-13 supports the Examiner's position, as does the specification at page 21 (see written description rejection below, with regard to this point).

The claim is also indefinite because part (c) says that a "substantial therapeutic activity" must be maintained, however there is no corresponding limitation earlier in the claim. It is noted that the claim has been amended to require a therapeutic activity, but this does not provide antecedent basis for a "substantial therapeutic activity". Even if it did, "substantial" is a relative term, the metes and bounds of which cannot be determined.

Claim 35 has been amended to refer to "native" thrombopoietin. First, "native" may mean non-denatured, or alternatively naturally occurring. If the latter is intended, the claim is

further indefinite because without a description of all TPO occurring in nature, one could not determine whether a given TPO were or were not a product of nature. The claim is also indefinite as it is not clear whether or not all of the amino acids of SEQ ID NO: 2 must be present, or whether any collection of such would meet the metes and bounds of the claim.

With further respect to claim 35, the recitation that the change "reduces an immune response" is a relative limitation, and would depend on the nature of the peptide, the species, genotype and health of the individual to whom it is administered, such that the metes and bounds of the claim cannot be determined. Claim 35 is also indefinite for the use of the term "substantial" for reasons cited above.

Claim 35 is indefinite for reciting "native" thrombopoietin. The term could indicate having a "native" sequence, or alternatively that the protein is not denatured. Further, if applicants intend the former interpretation, as not all "native" TPO sequences have been discovered or characterized, the person of ordinary skill in the art would not be able to determine whether or not a given sequence was "native". Applicants traverse this rejection by asserting that one of ordinary skill in the art would be able to identify a native sequence. This argument has been fully considered but is not deemed persuasive because it is not supported by fact or reason, and does not address the issues raised above.

Due to the amendment of claim 35 to remove the term "immunodominant epitope", claim 38 is indefinite for lacking antecedent basis for that term.

Claim 44 is further indefinite for reciting a "modified" nucleic acid sequence, for the same reasons as applied to "modified" protein sequences, above.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 30 (as amended) 33, and newly introduced claim 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The

claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. With respect to claims 35, 38 and 43-48 the rejection is withdrawn in view of the amendments to the claims.

With respect to claims 23, 28 and 33 and 51 er, it is acknowledged that applicants hold a patent to a *method* of making such variants. However, as stated above, claim 23 is indefinite because it claims a therapeutic polypeptide with reduced immunologic activity without specification of the peptide in question, or specifically where it is modified. The claim is drawn to a concept, rather than to a particular polypeptide or set of polypeptides. As such, the metes and bounds of the claim cannot be determined, and no meaningful search of the prior art can be performed. In addition to being indefinite, the claim lacks adequate written description; there is no way the Examiner can envision what species would or would not fall within the metes and bounds of the claim. The concept of making such variants is not a *description* of the variants so found. In this case, there can be no conception prior to reduction to practice. Accordingly, the description fails to support the claims.

The identification of the immunodominant epitope is essential to the invention. The claim has been amended to recite that the identification is done by "contacting" the polypepide or fragments thereof with an antibody or population thereof from a naive human or animal or population thereof. Applicants point to the paragraph bridging pages 13-14 of the specification for basis for such. However, it remains that such description (which constitutes new matter, see below) does not recite sufficient method steps. Merely "contacting" will not detect immunodominant epitopes. Antibodies from a naïve population might or might not react with immunodominant epitopes, they might react with non-immunodominant epitopes. In fact this is addressed at page 18, which describes a screening process, concluding that the immunodominant epitope can be the only epitope that can be found to bind to the antibodies from a human subject or population thereof or a polypeptide can have more than one immunodominant epitope. However, there is no definition of what is intended by "immunodominant"; such is a relative term, such that one cannot determine what the process is. Finally, applicants point to page 21,

which states that a proprietary and non-specified algorithm is to be used, and that "the predicted epitopes are optionally also scored for the likelihood of binding to HLS DR and DQ alleles", without any guidance as to how such scoring is to be done. Accordingly, the invention is incompletely described.

Applicants argue at page 10 of their response to the effect that because the method is patented, that the polypeptides themselves are described. This argument has been fully considered but is not deemed persuasive because a method of modifying a protien does not describe the end product. It remains, as set forth in the rejection under 112, second paragraph, that one cannot envision the encompassed polypeptides, and that a description of how to make them is not a constructive reduction to practice of the polypeptides that one would obtain. There is no showing of possession, constructive or actual, of the claimed polypeptides. Applicants argument of the case *Falkner v. Inglis* has been fully considered but is not deemed persuasive, as the claim therein is (a) not drawn to any polypeptide or virus, but specifically to a small family of poxviruses, which have conserved structures and functions, and (b) the essential regions of poxviruses have been characterized. Therefore, the breadth of the claim cited by applicants in no way corresponds to the breadth of the claims in question herein.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides or proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only thrombopoietin having alterations in the sequence at positions 318-332 (none of which would be expected to alter the biological activity of the protein) , but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 23, 30, 33 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification is enabled in scope only for antibodies obtained from naïve individuals with autoimmune diseases.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:
1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification does not enable the identification of immunodominant epitopes using antibodies from naïve humans or animals. By definition in the specification, such subjects have not been administered the protein in question. Accordingly, such antibodies would have to be present because of (a) cross reaction of a pre-existing antibody with the protein in question, or (b) autoimmune disease. Neither of these circumstances is predictable. The specification provides no guidance as to how to obtain such antibodies from naïve subjects, in the sense that there is no guidance as to how to select subjects that would be expected to have such antibodies.

Autoimmune diseases to single proteins are extremely rare, in the sense that there are only a very limited number of such diseases, and therefore only a very limited number of proteins to which antibodies could be obtained. Further, the proteins to which antibodies occur in autoimmune disease are generally not, considered to be therapeutic proteins. Therefore the vast majority of autoantibodies would not be within the metes and bounds of the claims. The specification does not disclose obtaining antibodies from autoimmune subjects, nor are specific proteins listed in the specification to which one would expect such autoantibodies. Further, there is no autoimmune disease known to be associated with TPO specifically. Three are no working examples in which antibodies from naive subjects were obtained or used. The word "naive" only occurs once in the specification, at paragraph [0066] of the PGPUB. Accordingly, the specification is only enabled for naïve subjects with autoimmune diseases, only for those proteins to which the subject is autoimmune. It is noted that there is insufficient written description in the specification to support such claims, such that amendment of the claims to reflect such would be considered new matter.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 23, 33, 35, 43-48 and 51 and are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6608183 (Cox et al.).

Cox teaches modification of proteins to introduce cysteine residues in non-essential regions of the proteins. The cysteines can then be used for coupling to polyethylene glycol or other moieties. Attachment of polyethylene glycol is generally recognized in the art as being effective to make a protein less immunogenic. With specific reference to TPO, Cox teaches at paragraph DETX (117)that preferred sites for introduction of cysteine residues include T312, T314, S315, N319, T320, S321, T323, S325, Q326, N327, L328, S329, Q330, E331 and G332. Note that Cox's numbering differs from applicants in that residue 332 of Cox corresponds to residue 353, or the final amino acid of the mature protein, such that the first residue of SEQ ID NO: 2 (331-348) of this application corresponds to residue 310-327 of Cox, and SEQ ID NO:1 of the instant application corresponds to residues 318-332 of Cox. Therefore, numerous of the residues disclosed by Cox as cited above meet the limitations of claim 35. The person of ordinary skill in the art is well aware that addition of polyethylene glycol extends the half-life of proteins, as mentioned by Cox at paragraph 63 of the detailed description. Accordingly, Cox et al. anticipates the claims.

Applicants traversal that Cox does not disclose substitution, as opposed to addition of cysteine residues is factually incorrect; see paragraph 30 of the Brief Summary of the Invention, which states: "The present invention provides "rules" for determining a priori which regions and amino acid residues in members of the GH supergene family can be used to introduce or substitute cysteine residues …."

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 30, 33 and 51 are rejected under 35 U.S.C. 103(a) as being obvious over WO 92/10755 (Lovborg et al.), cited by applicants in view of U.S. Patent No. 5,422,339 (Eisenbarth et al.)

Lovborg et al. disclose a method of mapping immunodominant epitopes of desired proteins, and then producing less immunogenic variants of such proteins by recombinant DNA methods; see abstract and claims, especially claims 1, 5, 6, 18 and 19. Preferred proteins to be mutated include "medicinal proteins, e.g. hormones, e.g. insulin, HCG, or growth hormone, or medicinal enzymes...", and "interleukins, or interferons, are of special interest." See page 5. The epitope mapping is performed using antibodies, see pages 6-7. They state that the epitopes in the protein are changed by genetic engineering or chemical modification through 'well established techniques' see page 6. Exemplified species were made via substitution or deletion of residues, see page 10. Human proteins are preferred species, see page 2. Since Lovborg teaches medicinal proteins, pharmaceutical compositions are clearly envisioned. Lovborg does not disclose the use of antibodies from naïve individuals.

Eisenbarth et al. disclose autoantibodies to insulin. It is notoriously old and well known in the art that insulin is administered to diabetics, i.e. is a therapeutic protein.

Accordingly, It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the insulin autoantibodies disclosed by Eisenbarth in the method of Lovborg, for the purpose of formulating a non-immunogenic or less immunogenic insulin, to treat patients with autoimmune diabetes. Accordingly, the invention, taken as a whole, is *prima facie* obvious.

Applicants, starting at page 16 of the response, traverse this argument on the bases that Lovborg does not disclose identification and modification of *immunodominant* epitopes, nor only one thereof. This argument has been fully considered but is not deemed persuasive because clearly Lovborg's epitopes meet the limitations of being *immunodominant* in view of the instant specification and rejections herein, and the language "at least one of said epitopes is changed through mutation..." as found in claim 1 clearly encompasses a change in only one immunodominant epitope.

Claims 23, 30, 33 and 51 are rejected under 35 U.S.C. 103(a) as being obvious over WO 92/10755 (Lovborg et al.), cited by applicants in view of in view of WO99/53038 (Estell et al., cited by applicants ).

The teachings of Lovborg et al. are cited above. Lovborg does not disclose the use of antibodies from naïve individuals.

Estell et al. teach a method of identifying immunodominant epitopes using T cells from naive human individuals, see page 4-5, for the purpose of preventing an initial reaction to a protein.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Lovborg et al. to use antibodies from naive individuals in view of the disclosure by Estell et al. that mapping epitopes using materials from naive individuals can be useful in preventing initial reactions to therapeutic proteins. Accordingly, it would have been obvious to use antibodies from naive individuals to prevent such initial reactions, as well as from dosed individuals, for the purpose of preventing subsequent reactions. The person of ordinary skill in the art would appreciate that it is the net result that would be of importance, and the order in which the steps were performed (naive vs. dosed)

would not be of significance. Thus, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al., U.S. Patent No. 6,608,183.

Claim 39 contains the limitation that the modification to TPO *consists* of a deletion of residues 339-353.

The teachings of Cox et al. are summarized above. Of specific interest is the teaching that the cysteine-added variants are also provided in the context of the natural human protein or a variant protein that is truncated between amino acids 147 and the C-terminus of the natural protein, G332. Note that Cox's numbering differs from applicants in that residue 332 of Cox corresponds to residue 353, or the final amino acid of the mature protein. Given the limited number of places for truncation, any one of the specific deletions encompassed is obvious. Accordingly, the claimed species is *prima facie* obvious.

The Examiner's position is supported by the recent finding by the Supreme Court in *KSR v. Teleflex, Inc.* (82 USPQ 2d 1385, 4/30/2007), which held that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (See 82 USPQ2d at 1397.) In this instance, there are a limited number of deletions that would be expected to retain biological activity, i.e. known options, each of which would have been expected to retain therapeutic activity.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.
Primary Examiner
Art Unit 1647